

REMARKS

Reconsideration of the present application, as amended, is respectfully requested. The application, as amended, includes claims 1-15, 19, 20, 22, 23, 26-28, 31, 32 and 34-40, pending and under consideration.

Remarks Regarding Restriction Requirement as Between Group I and Group II Claims

As an initial matter, the Examiner has previously asserted a restriction requirement, identifying Group I as including claims 1-15, 19-20, 22-23, 26-28 and 31-40, and Group II as including claims 16-18, 21, 24-25 and 29-30, whereupon Applicants elected Group I with traverse. The Examiner has now made this requirement final. As such, claims 16-18, 21, 24-25 and 29-30 of non-elected Group II, have been withdrawn by the Examiner.

Remarks Regarding Restriction Requirement as Between Nucleotide and Amino Acid Sequences and Regarding Objection to Claims as reciting Non-elected Sequences

The Examiner has also previously asserted a restriction requirement as between the multiple nucleotide sequences and amino acid sequences set forth in the Sequence Listing. Applicants also traversed this requirement, and the Examiner has also made this requirement final. The Examiner has now objected to claims 8, 12, 28, 35 and 40 because they recite nonelected sequences. Applicants respectfully traverse this objection, and request that the Examiner reconsider this restriction requirement and this objection in view of the following remarks. Upon reconsideration, Applicants respectfully request that the Examiner withdraw this objection, and also withdraw the restriction requirement as between the sequences set forth in these claims.

Applicants submit that, in keeping with the guidance set forth in Section 803.04 of the Manual of Patent Examining Procedure (“MPEP”), it is not appropriate in the present case to

require restriction between the sequences set forth in claims 8, 12, 28, 35 and 40. Applicants acknowledge the position of the Patent Office that nucleotide sequences encoding different proteins are structurally distinct chemical compounds, are considered to be unrelated to one another, are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121, and are presumed to represent independent and distinct inventions; however, MPEP 803.04 indicates that a restriction requirement should still not be imposed in cases such as this. In particular, MPEP 803.04 states that:

[T]o further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Commissioner has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See *Examination of Patent Applications Containing Nucleotide Sequences*, 1192 O.G. 68 (November 19, 1996).

It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction.

In view of this guidance from the MPEP, and the fact that the present invention recites only nine (9) amino acid sequences and nine (9) corresponding polynucleotide sequences, Applicants submit that it is proper to withdraw the restriction requirements as between the sequences in the present application. For this reason, in addition to the reasons set forth in the prior response, Applicants respectfully submits that it is proper to examine all of the sequences in the present application together, notwithstanding that they constitute separate and distinct inventions. Applicants therefore respectfully request withdrawal of this restriction requirement, and withdrawal of the objection to claims 8, 12, 28, 35 and 40.

Remarks Regarding Objection to Claims as Depending from Withdrawn Claims

The Examiner has also objected to claims 19, 20, 22 and 26 because they depend from claims withdrawn from consideration as being directed to non-elected inventions. In response to this objection, Applicants have amended these claims to place them in independent form. Applicants submit that, upon entry of these amendments, the objection to these claims is overcome.

Remarks Regarding Rejection of Claims Under 35 U.S.C. §112, first paragraph (Written Description)

In the outstanding Office Action, there is asserted a rejection of claims 1-15, 19-20, 22-23, 26-28 and 31-40 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states in the Action that, “The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.”

As a preliminary observation, Applicants would note that the Examiner has characterized the subject matter of the pending claims overly broadly. In this regard, the Examiner has alternately stated that the claims encompass “a polynucleotide encoding any functional GAD enzyme of undefined structure” and that the claims encompass “a GAD enzyme comprising any amino acid sequence having at least about 60% identity to SEQ ID NO:2, and including any polynucleotide that hybridizes under moderately stringent conditions to SEQ ID NO:1...” (Action, page 4). These statements suggest that the Examiner believes each of the pending claims either lacks sufficient structural definition or lacks sufficient functional definition. Applicants respectfully traverse any such suggestion.

In traversal of the Examiner's characterization of the claims, Applicants respectfully submit that each of the pending claims includes sufficient structural AND functional definition to satisfy the written description requirement of section 112, first paragraph. Indeed, given the well-known characteristics of GAD enzymes described in the literature prior to the filing of the present application, Applicants submit that, at the time the present application was filed, the very statement of the name "GAD" conveyed a significant amount of information to a person of ordinary skill in the art regarding structural and functional characteristics of the enzyme. Enclosed herewith is a Declaration Under 37 C.F.R. §1.132 (hereafter "Declaration") that provides evidentiary support for this assertion (Declaration, paragraph 4). The Examiner includes in the outstanding Action a summary of several structural characteristics indicated in the prior art to be associated with functional plant GAD enzymes. Applicant submits that, at the time the present application was filed, these structural characteristics were known to persons of ordinary skill in the art. (Declaration, paragraph 4). An excerpt from page 5 of the outstanding Action is set forth below:

For example, Turano et al. teach that GAD peptides are divided into 3 distinct regions: (1) a small amino terminal variable region of unknown functional significance, (2) a largely conserved middle region encoding GAD enzymatic [sic] activity, and (3) a small carboxy terminal variable region encoding a calmodulin binding domain. Turano et al. also teach that the *Arabidopsis* GAD1 and GAD2 sequences comprise a Ser-X-X-Lys amino acid motif common among PLP-requiring enzymes, and that the Ser-X-X-Lys motif is conserved in both identity and position as compared to GAD enzymes of petunia, tomato, and the *gadA* and *gadB* genes of *E. coli*. (Citation omitted).

The Examiner states in the outstanding Action that, "In light of GAD's requirement for specific structural characteristics, amino acid sequences having at least about 60% identity to SEQ ID NO:2 that correspond to functional plant GAD enzymes are not described." In

traversal, Applicants submit that the structural characteristics identified by the Examiner were known, at the time the present application was filed, to be associated with functional GAD enzymes. It is therefore unnecessary and redundant to include this information in the specification or in the claims. A person of ordinary skill in the art, upon considering the language in the claims will immediately understand the structural features that are known to be present in functional GAD enzymes. Thus the additional recitation of amino acid identity levels and polynucleotide hybridization requirements simply add further structural definition to claims that already include sufficient structural definition due to the knowledge in the relevant art.

It is also stated in the outstanding Action that, “polynucleotides that encode any functional GAD enzyme of undefined structure obtained from any plant species are not adequately described, as a representative number of species that would support the description of such a broad genus are not disclosed.” Applicants submit first that this characterization of the claims as lacking structural definition is improper for the same reasons that are set forth above. The claims do recite sufficient structural definition that a person of ordinary skill in the art would immediately recognize that the claims properly describe the invention in terms of structure and function, and that Applicants, at the time the application was filed, were in possession of the claimed invention. (Declaration, paragraph 4). Secondly, Applicants submit that they have described in the specification a representative number of species supporting the claimed genus. (Declaration, paragraph 5). As stated by the Court of Appeals for the Federal Circuit in Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), a description of a genus of cDNAs may be achieved by means of a recitation

of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. This reasoning applies equally well to claims reciting amino acid sequences. It is also worthy of note that the specification of the patent under review in University of California describes only a single cDNA, i.e., a cDNA encoding rat insulin. In contrast, the present specification discloses and describes in detail a variety of sequences that constitute a representative number of sequences of the claimed genus. It is stated in the outstanding Action that, “the specification describes only nine specific sequences obtained from four different species of dicotyledonous plants (Arabidopsis, tobacco, petunia and tomato) that are said to correspond to GAD enzymes.” Applicants submit that, upon proper consideration of the actual breadth of the claimed subject matter, which is not overly broad as suggested in the Action, the description of nine (9) specific sequences within the claimed genus far exceeds a “representative number of species” and is much more than a minimum number necessary to support the claimed genus.

It is also stated in the outstanding Action that, “the specification does not describe the extent to which, if any, these [nine] sequences are structurally and functionally related to one another.” In reply, Applicants again note that a person of ordinary skill in the art would readily understand the structural features of a GAD enzyme, would readily identify the sequences set forth in the Sequence Listing as GAD enzymes, and would be readily able to determine the level of structural similarity therebetween. (Declaration, paragraph 5). In addition, Applicants would refer the Examiner to the information set forth in paragraph 6 of the attached Declaration, which sets forth the structural relatedness of the nine sequences in terms of

percent sequence identity. Applicants also submit that the structural and functional relatedness of the sequences would have been apparent to a person of ordinary skill in the art at the time the present application was filed upon consideration of the specification. (Declaration, paragraph 6). As such, it is not necessary for this information to be reiterated in the specification and, indeed, it is axiomatic that the specification should not include information that is already generally known to a person of ordinary skill in the art. In this regard, MPEP §2164.01 states that, “A patent need not teach, and preferably omits, what is well known in the art.” (citations to multiple Federal Circuit decisions omitted).

It is also stated in the outstanding Action that, “the specification does not describe the structural characteristics of a modified GAD enzyme that does not include a functional autoinhibitory calmodulin-binding domain, even though the prior art indicates that specific but variable structural characteristics as [sic] associated with the calmodulin-binding domain of plant GAD enzymes.” Applicant submits that a modified GAD enzyme without a functional autoinhibitory calmodulin-binding domain is described in the specification in a manner that would be understood by a person of ordinary skill in the art. (Declaration, paragraph 7). Although calmodulin-binding domains of plant GAD enzymes, which are located in the carboxyterminal region of GAD, vary between different GAD sequences, this does not negate the fact that a person of ordinary skill in the art would understand and recognize a calmodulin-binding domain as such. (Declaration, paragraph 7). Indeed, given the high degree of conservation in the enzymatic domain of GAD, a person of ordinary skill in the art would readily recognize the enzymatic portion of a GAD sequence, and conclude that non-conserved residues at the carboxy-terminal end are to be excluded if it is desired to express a GAD

without the calmodulin-binding domain. Thus, based upon the present specification and information available in the art at the time the application was filed, a person of ordinary skill in the art would have known how to make and use the various aspects of the invention relating to GAD enzymes lacking a calmodulin-binding domain. (Declaration, paragraph 7).

At page 6 of the outstanding Action, the Examiner cites the University of California v. Eli Lilly and Co. case as clarifying how to apply the written description requirement. Applicants submit that when the analysis set forth in the University of California case is applied to the present case, the analysis unquestionably leads to a conclusion that the written description requirement is met in this case. In view of the level of knowledge and skill in the relevant art, the naming of a “GAD enzyme” in the present claims conveys sufficient information to a person of ordinary skill in the art regarding the structural characteristics of the claimed subject matter to distinguish it (i.e., a GAD enzyme) from other materials. This does not constitute “naming a type of material generally known to exist, in the absence of knowledge as to what the material consists of.” Rather, given the wealth of information in the literature regarding functional GAD enzymes, the naming of the material in the present application provides much information to a person of ordinary skill in the art regarding what the material consists of. In addition, Applicants provided in the specification descriptions of a representative number of species of the claimed genus, and one of skill in the art would be able to “visualize or recognize the identity of the members of the genus.” For all of these reasons, Applicants submit that the analysis set forth by the Court of Appeals for the Federal Circuit in the University of California decision requires a finding in the present case that the pending

claims satisfy the written description requirement. Applicants therefore respectfully submit that this rejection is overcome, and respectfully request that this rejection be withdrawn.

Remarks Regarding Rejection of Claims Under 35 U.S.C. §112, first paragraph (Enablement)

In the outstanding Office Action, claims 1-15, 19-20, 22-23, 26-28 and 31-40 are rejected under 35 U.S.C. §112, first paragraph, upon an assertion that the specification, while being enabling for multiple aspects of the invention as they relate to the GAD2 polynucleotide and GAD2 enzyme of SEQ ID NOS:3 and 4, does not reasonably provide enablement for various aspects of the invention as they relate to other GAD enzymes, such as the elected plant GAD enzyme of SEQ ID NO. The Examiner states in the Action that, “The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.”

Applicants believe that this rejection was made based upon an incomplete understanding of the claimed invention, in particular, an incomplete understanding of how the sequences set forth in the Sequence Listing of the present patent application are related to one another and the level of knowledge and skill of a person of ordinary skill in the pertinent art. As described above, the sequences set forth in the Sequence Listing of the present application are highly related to one another. Indeed, upon comparison of each of the sequences to each of the other sequences using the MacVector program and the default parameters set forth at page 23 of the present specification, the identities between the sequences range from 72.8% identity to 91.2% identity, and the various sequences have been shown to have multiple structural characteristics in common (Declaration, paragraphs 4-6). Furthermore, GAD enzymes featuring these sequences have been shown to be functional to catalyze the conversion of

glutamate to GABA. (Declaration, paragraph 9). As stated in paragraph 9 of the Declaration, several of the plant GADS set forth in the application have been successfully expressed as functional recombinant proteins in diverse species such as *E. coli*, insect cell lines and plants (Baum et al. 1993; Baum et al. 1996; Snedden et al. 1996; Turano and Fang, 1998; Yevtushenko et al. 2003; MacGregor et al. 2003), thus sequences having these degrees of primary sequence similarity have been shown to have the desired functional activity, i.e., catalyzing the GAD reaction, which is the conversion of glutamate to GABA.

The outstanding Office Action states that:

[T]he specification only discloses the phenotypes of plants transformed with polynucleotides encoding one type of GAD enzyme, the *Arabidopsis* GAD2 (nonelected SEQ ID NO:4) enzyme... The specification does not disclose the phenotypes of plants transformed with polynucleotides encoding other GAD enzymes, such as the *Arabidopsis* GAD1 (elected SEQ ID NO:2) enzyme, or GAD enzymes ... having at least about 60% identity to [SEQ ID NO:2] or by sequences that hybridize to SEQ ID NO:1 under moderately stringent conditions.

It is further stated in the action that the absence of this information defeats the enablement of the claims because, “the effect on transgenic plants of expressing a GAD enzyme, with or without a calmodulin-binding domain, at different levels or at different times or in different locations or under different conditions is unpredictable.” (Office Action, page 10). The Action then states the following two reasons that the effect is unpredictable:

- (1) “The effect is unpredictable because different levels of GAD and its product GABA have different effects on plants.” (citations omitted) (Office Action, page 10); and
- (2) “The effect on transgenic plants of expressing a GAD enzyme is also unpredictable because the level of GAD expression and GAD activity would be affected by multiple variables which include but are not limited to whether the GAD enzyme retained its calmodulin binding domain, the type of promoter and terminator used in the expression

vector, the plant species transformed by the expression vector, the type of tissue in which GAD is expressed, the stability of the mRNA transcribed from the GAD coding sequence, the translation efficiency of the mRNA, GAD stability, the availability of glutamate substrate and other substances, such as calcium and calmodulin and PLP, that would affect GAD activity.” (citations omitted) (Office Action, page 11).

In view of the above, the Examiner concludes that the full scope of the claimed invention is not enabled because:

- (1) “[T]he specification does not provide sufficient guidance for one skilled in the art to determine, without undue experimentation, which combinations of GAD enzymes and non-constitutive promoters would result in a level of GAD expression and/or activity that would produce a specific desired phenotypic effect in plants transformed therewith.” (Office Action, page 11); and
- (2) “[T]he specification does not provide sufficient guidance for one skilled in the art to determine, without undue experimentation, how to express a GAD1 enzyme in a manner that would produce specific phenotypic effects comparable to those produced in plants transformed with constructs comprising GAD2 sequences.” (Office Action, page 11).

Applicants traverse this rejection, and respectfully submit that each of the reasons for this rejection given in the Action is based upon an improper premise regarding the understanding of the invention by a person of ordinary skill in the art at the time the application was filed. Applicants do not dispute the Examiner’s assertion that the field of the present invention can be characterized as unpredictable; however, Applicants submit that the level of unpredictability associated with the present invention is merely that typical of performing any plant genetic transformation events, and does not require undue experimentation. (Declaration, paragraph 11). It is important to understand that biological systems by their nature include a degree of variability, and those skilled in the art understand that genetic transformation events produce variable results. In other words, due to the well-documented phenomena of epigenetic

genetics (Qin et al. 2003; Meyer, 2000; Meyer 2003; Flavell, 1998) and position effects (van Leeuwen et al. 2001; Matzke and Matzke, 1998) when making transgenic plant lines, a plant transformation process is inherently variable. (Declaration, paragraph 11).

Notwithstanding this variability, a person of ordinary skill in the art, upon reading the present specification, would understand that excellent results of the invention can be achieved by over-expressing GAD in a plant in a manner whereby increased levels of GABA are produced, but whereby GABA is not overproduced at a level whereby the plant is stunted or sterile or otherwise has undesirable morphological characteristics. (Declaration, paragraph 11). In other words, the present specification clearly teaches to a person of ordinary skill in the art that transformation of a plant in accordance with the invention to achieve controlled enhancement of GABA production, i.e., GABA production at a higher level than a wild-type plant, but not so great as to produce stunting, sterility and the like, provides desired characteristics in the plant or plant tissues. When this information is considered together with the well-known identity and functionality of GAD enzymes, a person of ordinary skill in the art would readily appreciate that the present specification enables a skilled artisan to transform plants with functional GAD enzymes. (Declaration, paragraph 11). A person of ordinary skill in the art would further appreciate that, due to the inherent variability associated with plant transformation events, it is appropriate to make multiple transformed plants (preferably 25-50 or more) with a given construct, and then to select one or more plants that over-expresses the functional GAD enzyme at a desired level, i.e., does not over-express to a level that causes stunting or sterility or the like. While the specification includes data relating to plants transformed with one GAD construct, a person of ordinary skill in the art would reasonably

expect to be able to practice the full scope of the claimed invention, including use of constructs including other functional GAD enzymes, in view of the descriptions included in the specification. (Declaration, paragraph 11).

In view of the above, Applicants submit that the invention recited in the pending claims, as amended, is adequately enabled by the specification as required by 35 U.S.C. §112, first paragraph. Applicants therefore respectfully request withdrawal of this rejection.

Remarks Regarding Rejection of Claims Under 35 U.S.C. §112, second paragraph

In the outstanding Office Action, claims 8, 12, 28, 31, 32, 34, 35, 38 and 40 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Without acquiescing in the rejection, in order to facilitate allowance of the present application Applicants have amended claims 8, 28, 31, 32, 34 and 38 to remove the wording identified by the Examiner to be objectionable. As such, Applicants respectfully submit that the rejection is overcome with respect to these claims.

With reference to claims 12, 35 and 40, the Examiner states that these claims are indefinite in the recitation of “moderately stringent conditions.” In support of this rejection, the Examiner states that, “It is unclear what type of hybridization conditions would be ‘moderately’ stringent. Neither the claims nor the specification indicate specific hybridization conditions that are ‘moderately’ stringent. Furthermore, those skilled in the art would interpret ‘moderately’ differently.”

In reply, Applicant would draw the Examiner's attention to the specification at pages 22-23, wherein the following statements define "moderately stringent conditions" in a manner that would be readily understood by a person of ordinary skill in the art:

In another embodiment, the polynucleotide has a sequence that encodes a functional plant GAD enzyme, and has a sequence sufficiently similar to the coding region of a reference polynucleotide that it will hybridize therewith under moderately stringent conditions. This method of determining similarity is well known in the art to which the invention pertains. Briefly, moderately stringent conditions are defined in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed. Vol. 1, pp. 101-104, Cold Spring Harbor Laboratory Press (1989) as including the use of a prewashing solution of 5X SSC (a sodium chloride/sodium citrate solution), 0.5% sodium dodecyl sulfate (SDS), 1.0 mM ethylene diaminetetraacetic acid (EDTA) (pH 8.0) and hybridization and washing conditions of 55°C, 5x SSC.

In view of this description in the specification, Applicants submit that a person of ordinary skill in the art would understand the meaning of "moderately stringent conditions" to be clear and definite as required by 35 U.S.C. §112, second paragraph. (Declaration, paragraph 13). Applicants therefore respectfully request withdrawal of this rejection.

Remarks Regarding Rejection of Claims Under 35 U.S.C. §101

In the outstanding Office Action, claims 14, 22, 37 and 38 are rejected under 35 U.S.C. §101. It is asserted in the Actin that "the claimed invention is directed to non-statutory subject matter." The Action also states that, "Amendment of the claims to indicate that the progeny comprise the DNA construct introduced into the parent plant would overcome the rejection." In order to facilitate allowance of the present application, Applicants have amended the claims in the manner suggested by the Examiner. As such, Applicants respectfully submit that this rejection is overcome, and respectfully requests withdrawal thereof.

Remarks Regarding Rejection of Claims Under 35 U.S.C. §102(b)

In the outstanding Office Action, claims 31-40 are rejected under 35 U.S.C. §102(b) as being anticipated by Baum et al. (EMBO J., 17 June 1996, Vol. 15, No. 12, pages 2988-2996). Without forfeiting the right to later pursue the subject matter of the original claims 31-40, Applicants have above-requested entry of amendments, resulting in amended claims 31-32 and 34-40 that clearly recite subject matter that is not anticipated by the Baum et al. article. In this regard, claim 31 is amended to recite that, “the GAD enzyme does not include a functional autoinhibitory calmodulin-binding domain.” Claim 31, as amended, recites subject matter that is novel over Baum et al. because the only transformed plant described by Baum et al. that expressed a GAD enzyme that does not include a functional autoinhibitory calmodulin-binding domain exhibited significant loss of growth characteristics, yield, reproductive function or other morphological or agronomic characteristic compared to a non-transformed plant, which is expressly excluded by Applicants’ claim 31, as amended. (Declaration, paragraph 14). (See Baum et al. page 2989, column 1, first full paragraph). As stated above, the present invention involves the recognition that, although excessive overproduction of GABA in a plant causes stunting and other undesirable agronomic and/or morphological characteristics, non-excessive overproduction of GABA in a plant results in beneficial characteristics, such as, for example, enhanced stress resistance or other desirable morphological and/or agronomic characteristics. (See specification, page 13, lines 16-21). A desirable level of overproduction of GABA is achieved in the method of claim 31, as amended, by transforming a plant that constitutively expresses a de-regulated GAD enzyme, and then selecting a plant that does not exhibit

stunting, sterility and/or other undesirable characteristics that are indicative of excessive overproduction of GABA.

Independent claims 38 and 40 have been amended in a manner similar to claim 31. It is therefore believed that these claims are also in condition for allowance. Claims 32 and 34-37 are dependent upon claim 31 and are believed to be allowable at least for the same reasons that claim 31 is allowable, and for other reasons. Similarly, claim 39 is dependent upon claim 38, and is believed to be allowable at least for the same reasons that claim 38 is allowable, and for other reasons.

In view of the above, Applicants submit that the Baum et al. reference cannot properly be found to anticipate claims 31-32 and 34-40, as amended. Applicants therefore respectfully request withdrawal of this rejection.

Remarks Regarding Rejection of Claims Under 35 U.S.C. §103(a)

In the outstanding Office Action, claims 1-15, 19-20, 22-23 and 26-27 are rejected under 35 U.S.C. §103(a) as being unpatentable over Baum et al. (EMBO J., 17 June 1996, Vol. 15, No. 12, pages 2988-2996) in view of McKenzie et al. (Plant Physiology, March 1998, Vol. 116, No. 3, pages 969-977). In traversal of this rejection, Applicants submit that the Examiner has not pointed out any motivation in the references, or in the literature as a whole, to combine the references in the manner suggested by the Examiner to be obvious.

In the outstanding Action, the Examiner notes that Baum et al. describe tobacco plants transformed with a vector comprising a constitutive CaMV 35S promoter operably linked to a polynucleotide that encodes a wild type petunia plant GAD enzyme, and tobacco plants transformed with a vector comprising a constitutive CaMV 35S promoter operably linked to a

polynucleotide that encodes a mutant petunia plant GAD enzyme that lacks a calmodulin-binding domain.

The Examiner also relies upon McKenzie et al. as follows:

McKenzie et al. teach the use of a copper controllable root specific promoter to selectively increase the production of the growth affecting compound cytokinin in response to a signal in plants transformed with a DNA construct comprising a non-constitutive promoter operably linked to a polynucleotide encoding isopentenyl transferase. The plants taught by McKenzie et al. exhibited phenotypic effects associated with cytokinin (loss of apical dominance and delayed leaf senescence), but they did not exhibit the morphological abnormalities exhibited by plants transformed with DNA constructs comprising a constitutive promoter operably linked to a polynucleotide encoding isopentenyl transferase. (Citations omitted).

In support of this rejection, the Examiner states that:

[I]t would have been prima facie obvious to one skilled in the art at the time the invention was made to express in a transgenic plant a functional plant GAD enzyme as taught by Baum et al. using non-constitutive promoter [sic] such as the copper controllable root specific promoter taught by McKenzie et al., for the purpose of controlling the phenotypic effect associated with the growth affecting properties of GAD enzyme activity by controlling the time and/or location of GAD enzyme expression, without any surprising or unexplained results. (Office Action, Page 19).

Applicants respectfully traverse this rejection because the Examiner has not identified any motivation in the cited references or any other prior art to combine the references as suggested in the Action. The Examiner has simply characterized what the reference teach, and leapt straight to a conclusion that one skilled in the art would be motivated to combine them, with no explanation or analysis as to where such a motivation arises. To the contrary, Applicants submit that there is no direct suggestion in either reference to combine their teachings, and there is also no indirect suggestion that could be considered to be a motivation to combine the teachings of the references. (Declaration, paragraph 17).

Applicants submit that, rather than providing any motivation to combine the teachings of the references as suggested by the Examiner, the Baum et al. reference actually teaches away from the present invention, and would actually discourage a person of ordinary skill in the art from performing work that would lead to the present invention. (Declaration, paragraph 17). The results of the Baum et al. work can be summarized as follows:

- (1) plants transformed with a normal GAD (with calmodulin-binding domain) under the control of a constitutive promoter do not have increased GABA levels *in vivo* (see Baum et al., page 2993, column 2, first partial paragraph), and have morphology indistinguishable from that of wild-type plants; and
- (2) plants transformed with a mutant GAD lacking a calmodulin-binding domain under the control of a constitutive promoter exhibit above-normal GABA levels *in vivo* (see Baum et al., page 2993, column 2, first partial paragraph), and are stunted, sterile, and featured other undesirable morphologic characteristics.

The message from this reference to a person of ordinary skill in the art at the time the present application was filed is that elevation of the GABA level in a plant is undesirable, and that transformation of a plant with a de-regulated GAD is therefore undesirable. (Declaration, paragraph 18). The reference also suggests that transformation of a plant with a normal GAD (i.e., a GAD including a functional calmodulin-binding domain) has no effect on the GABA levels in the plant or the morphology of the plant, and therefore provides no benefit to the plant. (Declaration, paragraph 18). Thus, a person of ordinary skill in the art would find no motivation in Baum et al. to transform a plant with a normal GAD or a de-regulated GAD under the control of a non-constitutive promoter, because he or she would expect the resulting plant to be either unchanged morphologically (if including the calmodulin-binding domain) or alternatively to respond to a signal by producing harmful, and perhaps lethal levels of GABA

in the tissues expressing the de-regulated GAD (if not including a functional calmodulin-binding domain). (Declaration, paragraph 18).

There is no suggestion in the references of record that there would be any desirable result from overexpressing GAD or overproducing GABA in plant tissues. (Declaration, paragraph 19). Without such a suggestion or motivation, there is no suggestion or motivation to combine the two references cited in the outstanding Action. As such, no *prima facie* case of obviousness of claims 1-15, 19-20, 22-23 and 26-27 has been made, and Applicants respectfully request withdrawal of this rejection.

Closing

In view of the above, Applicants respectfully submit that the rejections stated in the outstanding Action are overcome and that the present application, as amended and including claims 1-15, 19, 20, 22, 23, 26-28, 31, 32 and 34-40, is in condition for allowance. Action to that end is respectfully requested. If there are any remaining issues that can be addressed telephonically, the Examiner is invited to contact the undersigned to discuss the same.

Respectfully submitted:



Gregory B. Coy
Reg. No. 40,967
Woodard, Emhardt, Moriarty,
McNett & Henry LLP
Bank One Center/Tower
111 Monument Circle, Suite 3700
Indianapolis, Indiana 46204-5137
(317) 634-3456